Therefore, the applicant respectfully requests the examiner accept the previously submitted declaration because it is not defective.

Claim Rejections - 35 U.S.C. § 112

The examiner has rejected claims 40 and 41 as being indefinite for failing to particularly point out and distinctly claim the subject matter that the applicant regards as the invention. The examiner points to the phrase "a known or equal amount" as being confusing because it is not clear what the "equal amount" is equal to.

The applicant disagrees with the examiner with regard to the assertion that the phrase "a known or equal amount" is confusing. In order to make a clear, and fair, reading of that portion of the claim, the clause must be read in its entirety, "making a plurality of standard preparations each containing a known but differing amount of said analyte or a counterpart thereof and *each containing a known or equal amount of said IRS*". Clearly the clause states that either each standard preparation contains a known amount of said IRS **or** each standard preparation contains an equal amount of said IRS (the claimed uncertainty in the phrase "equal amount" meaning that in the specified form, each standard preparation contains the same amount of IRS as every other standard preparation). Therefore, when making a fair reading of the claim, in its entirety, there is no confusion caused by using the phrase "a known or equal amount".

Further, the examiner has rejected claims 31, 33, 40, and 41 as being indefinite because the examiner feels that they are missing an essential method step. Specifically, section 31 c) recites "quantifying said analyte" but does not require quantifying the IRS. The examiner feels that it is not clear how a ratio of analyte signal to IRS signal can be made without quantifying the IRS.

The applicant disagrees with the examiner's contention that there is a missing essential method step. The examiner complains that section 31 c) recites "quantifying said analyte" but does not require quantifying the IRS. The applicant respectfully points to section 31 a) wherein the specimen is combined with a known concentration of IRS in order to calibrate subsequent steps. This combination of a known concentration of IRS with the specimen is the complained of missing step of quantifying the IRS. Further, the examiner complains that it is not clear how a ratio of analyte signal to IRS signal can be made without quantifying the IRS. The applicant respectfully points out that determining a ratio of two different signals is a simple operation that

can be taken from the ordinary dictionary meaning of the word "ratio". First, either a first signal height, or area contained within a first peak, is determined. Next, a second signal height, or area contained within a second peak, is determined. Finally, the first signal height/area is divided by the second signal height/area thus forming a ratio of the two signals. Because one of the signals is the IRS at a known concentration, as in the case claimed, the concentration of an analyte in an unknown may then be quantified. This is clearly taught in the specification of the instant application.

Finally, the examiner feels that it is not clear from step 31 b) whether the IRS is either captured *or* isolated.

As is taught in the instant specification, the act of capturing the analyte (and IRS) accomplishes the act of isolating the analyte (and IRS). The affinity reagent captures the analyte (and IRS) and simultaneously isolates them from any contents remaining in the specimen. Thus, the IRS is captured *and* isolated, as is stated in the claim.

Claim Rejections - 35 U.S.C. § 103

The examiner has rejected claims 31, 33, 40, and 41 as being unpatentable over Van Ginkel et al., of record, in view of US Patent No. 5,707,799 or US Patent No. 4,743,561. The examiner states that the claims are drawn to a method for quantifying an analyte in a specimen comprising combining an internal reference species (IRS) in a known concentration to normalize all subsequent steps with the analyte in the specimen, capturing and isolating said analyte by combining the IRS-containing solution with an affinity reagent, quantifying said analyte using mass spectrometric analysis to resolve distinct signals for said analyte and said IRS to determine the ratio of the analyte signal to the IRS signal wherein said quantifying step further comprises using working curve analysis which comprises first obtaining a mass spectrum of a first portion of said IRS containing specimen then making a plurality of standard preparations each containing a known but differing amount of said analyte and each containing a known or equal amount of said IRS, then obtaining respective mass spectra of each whereby said respective mass spectra provide a working curve relationship of mass spectra relative to analyte concentration and then using said first mass spectrum and the standard preparation mass spectra working curve relationship to quantify said analyte.

The examiner contends that Van Ginkel et al. teaches a method for quantifying an analyte in a specimen comprising capturing and isolating an analyte by combining it with an affinity reagent, combining an IRS, an isotopically labeled internal standard for quantification and quality control in a known concentration with the captured and isolated analyte to calibrate all subsequent steps with the analyte in the specimen, wherein the processed specimen is analyzed by mass spectrometric analysis which resolves distinct signals for the analyte and for the IRS wherein the quantification of the analyte is determined by the ratio of the analyte to the internal standard (that is the first mass spectrum of a first portion of the IRS containing specimen) and the quantification procedure used includes a linear calibration curve which is fitted with the ratio of abundance of the ions in question (i.e. tert-butyl-beta-agonists/internal standards) as the independent variable and the concentration of standard (ng/injection vial) as the dependent variable which procedure yields linear calibration curves with an intercept not significantly different than zero which inherently requires a plurality of standard preparations each containing a known but differing amount of said analyte and each containing a known or equal amount of said IRS to produce said linear calibration curve.

The examiner states that Van Ginkel et al. teaches as set forth above, but does not teach a method wherein the specimen is combined with an internal reference species of known concentration prior to the capturing and isolating step wherein the analyte and the IRS are captured and isolated.

The examiner points to US Patent No. 5,707,799 as teaching a method for quantitative determination of analytes in test samples comprising the steps of using a control means to verify an assay result wherein the test sample containing the analyte is contacted with a predetermined amount of labeled reagent to form a mixture containing an analyte/labeled reagent complex, the resulting mixture contacts a capture site containing an immobilized anti-analyte specific binding member that binds the analyte/labeled reagent complex which is the test sample capture site and teaches that the complex can be used to establish a positive control (at col. 13, line 54 to col. 14, line 31).

US Patent No 5,707,799 is not applicable to the present application. The portion of '799 the examiner cites as a method of quantitative determination of analytes in test samples is really a method for determining whether a positive test result should be believed. A clear reading of col.

13, line 54 to col. 14, line 31 indicates that the cited method "comprises a confirmatory assay" (col. 13, line 55) and that

> "[a] detectable signal at the positive control capture site confirms that the assay reagents are functional and the test result valid. For example, when no analyte is present in a test sample, the negative result of the test sample is confirmed as a valid test result when the positive control capture site has a detectable signal and the test sample site has not detectable signal. When analyte is present in a test sample, the positive result of the patient sample is confirmed as a valid test result when the positive control capture site has a detectable signal and the test sample capture site has detectable signal. No detectable signal at the positive control capture site itself, indicates either that the labeling system's sample have degraded or that other factors in the test sample have interfered with the biding of the labeled reagent to the positive control reagent or with the binding of the labeled positive control complex ...." (Col. 14, lines 14-29)

Thus, it is clear that the cited method does not teach a method of quantitative determination of analytes in test samples. Indeed, while it uses a predetermined amount of labeled reagent, the first step of the method has an indeterminate amount of the labeled reagent bound by analyte in the mixture, the second step also has an indeterminate amount of the labeled reagent bound by a positive control reagent, which may be an analyte identical to that of the test sample. Thus, since two different indeterminate amounts of labeled reagent are bound in two different steps, quantitation of the test sample is not possible. Therefore, this patent is not applicable as prior art to the instant invention and the '799 patent in combination with Van Ginkel et al. does not provide all of the claimed elements rendering the claims obvious.

The examiner also points to US Patent No. 4,743,561 as being applicable to the instant rejection, although being drawn specifically to fluorometric assays. The examiner states that this patent teaches that it is well recognized that in order to maximize the sensitivity and specificity of an assay, inhibiting and interfering factors must be compensated for by using an internal standard whereby the standard is added to an aliquot of sample and the entire assay procedure is carried out using the aliquot containing the internal standard (in col. 2, lines 50-59).

In the '561 patent, as the examiner states above, the practitioner includes an internal standard to overcome problems with impurities inhibiting and interfering with the fluorometric

assays. The present invention utilizes an internal standard to quantify the amount of analyte present in the sample, not to overcome problems with impurities. This is a major difference, and distinguishable, between the fluorometric analysis of the '561 patent and the present invention. In mass spectrometry, the analysis method claimed in the present invention, unwanted species have different masses, thus impurities or interferences are found in different positions on the spectra. An interfering species, by definition, would necessarily have to have the same mass as the analyte, a situation that virtually never occurs. This means that degradation in signal due to unwanted species are not a problem solved by the inclusion of an internal standard. It must be remembered that the internal standard of the present invention is included for quantitation of the analyte in the sample. Moreover, in mass spectrometry, the analytical method of the present invention, the addition of standards will actually decrease detection sensitivity and not increase it. Therefore, one of ordinary skill in the art, reading the '561 patent could not read it to fairly teach quantitation, but increased sensitivity of fluorescence assays. Thus, the '561 patent in combination with Van Ginkel et al. does not provide all of the claimed elements rendering the claims obvious.

The examiner contends that it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to have combined the methods of Van Ginkel et al. and the methods of US Patent No. 5,707,799 or US Patent No. 4,743,561 in order to produce an assay method wherein a standard was included in the immunoisolation step of Van Ginkel et al. because US Patent No. 5,707,799 clearly teaches that inclusion of a standard labeled reagent is useful for establishing a positive control and because US Patent No. 4, 743,561 teaches that it is well recognized that internal standards are useful for maximizing sensitivity and specificity of an assay. One of ordinary skill in the art would have been motivated to provide an internal standard in the analyte mix because US Patent no 4,743,561 specifically teaches that inhibiting and interfering factors must be compensated for by using an internal standard in the assay aliquot.

The applicant reasserts the arguments above. Nothing in the '799 or the '561 patent teach or suggest combination with a method, such as taught by Van Ginkel et al., to provide a quantitative measure of an analyte as is claimed in the present invention where an analyte and a known amount of IRS are mixed, then captured and isolated, and finally measured using mass spectrometry to provide a quantitative measure of the analyte by using a ratio of signals for the analyte and the IRS, as is claimed in the present invention.

Conclusion

The applicant has discussed and distinguished the examiners rejections above and pointed out the patentable differences between the present invention and the combinations cited by the examiner. Therefore, the applicant respectfully requests that the examiner withdraw all of the instant rejections and allow the claims to pass to issuance.

Respectfully submitted,

Date: 7/24/00

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